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ORIGINAL ARTICLE

Upadacitinib for moderate-to-severe atopic dermatitis: Stratified analysis from three randomized phase 3 trials by key baseline characteristics

J. P. Thyssen[1] | D. Thaçi[2] | T. Bieber[3,4] | M. Gooderham[5] | M. de Bruin-Weller[6] | W. Soong[7] | K. Kabashima[8] | S. Barbarot[9] | P. C. Luna[10] | J. Xu[11] | X. Hu[12] | Y. Liu[12] | E. M. Raymundo[12] | B. M. Calimlim[12] | C. Nduaka[12] | A. Gamelli[12] | E. L. Simpson[13]

[1]Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

[2]Institute and Comprehensive Center Inflammation Medicine, University of Lübeck, Lübeck, Germany

[3]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany

[4]Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

[5]SKiN Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough, Ontario, Canada

[6]National Expertise Center of Atopic Dermatitis, Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

[7]AllerVie Health – Alabama Allergy & Asthma Center and Clinical Research Center of Alabama, Birmingham, Alabama, USA

[8]Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[9]Department of Dermatology, Nantes Université, CHU Nantes, Nantes, France

[10]Servicio de Dermatología, Hospital Alemán, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina

[11]Huashan Hospital, Fudan University, Shanghai, China

[12]AbbVie Inc., North Chicago, Illinois, USA

[13]Department of Dermatology, Oregon Health and Science University, Portland, Oregon, USA

Correspondence
E. L. Simpson, Department of Dermatology, Oregon Health and Science University, 3303 SW Bond Ave, South Waterfront Center for Health and Healing Building 1, Portland, OR, USA.
Email: simpsone@ohsu.edu

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AbbVie Inc.

Abstract

Background: Atopic dermatitis (AD) is a heterogeneous inflammatory skin disease with different clinical phenotypes based on factors such as age, race, comorbidities, and clinical signs and symptoms. The effect of these factors on therapeutic responses in AD has only been scarcely studied and not for upadacitinib. Currently, there is no biomarker predicting response to upadacitinib.

Objectives: Evaluate the efficacy of the oral Janus kinase inhibitor upadacitinib across patient subgroups (baseline demographics, disease characteristics and prior treatment) in patients with moderate-to-severe AD.

Methods: Data from phase 3 studies (Measure Up 1, Measure Up 2 and AD Up) were utilized for this post hoc analysis. Adults and adolescents with moderate-to-severe AD were randomized to receive once daily oral upadacitinib 15 mg, upadacitinib 30 mg or placebo; patients enrolled in the AD Up study received concomitant topical corticosteroids. Data from the Measure Up 1 and Measure Up 2 studies were integrated.

Results: A total of 2584 patients were randomized. A consistently greater proportion of patients achieved at least 75% improvement in the Eczema Area and Severity Index, a 0 or 1 on the validated Investigator Global Assessment for Atopic Dermatitis, and improvement in itch (including an achievement of a reduction of ≥4; and score of 0/1 in Worst Pruritus Numerical Rating Scale) with upadacitinib compared with placebo

at Week 16, regardless of age, sex, race, body mass index, AD severity, body surface area involvement, history of atopic comorbidities or asthma, or previous exposure to systemic therapy or cyclosporin.

Conclusions: Upadacitinib had consistently high skin clearance rates and itch efficacy across subgroups of patients with moderate-to-severe AD through Week 16. These results support upadacitinib as a suitable treatment option in a variety of patients.

TRIAL REGISTRATION

ClinicalTrials.gov Identifiers: NCT03569293 (Measure Up 1), NCT03607422 (Measure Up 2) and NCT03568318 (AD Up).

INTRODUCTION

Atopic dermatitis (AD), a common, chronic inflammatory skin disease, is characterized by eczematous skin lesions and intense itch. Atopic dermatitis has a complex aetiology and a wide gamut of phenotypes based on multiple factors, including age, race, disease chronicity, clinical signs and symptoms and comorbidities (e.g. asthma).[1–3] Patient age, age of onset, weight, body mass index (BMI), presence of comorbidities and previous systemic therapy use are known to affect treatment outcomes in other immune-mediated inflammatory skin conditions, such as psoriasis,[4] but whether these factors impact therapeutic responses in AD is largely unknown.

Multiple cytokines implicated in AD signal through the Janus kinase (JAK) pathway.[5] Upadacitinib is an oral JAK inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, and tyrosine kinase 2.[6] The efficacy and safety of upadacitinib with and without topical corticosteroids (TCS) for the treatment of adolescent and adult patients with moderate-to-severe AD were demonstrated in three phase 3 randomized, placebo-controlled studies as well as a phase 3 comparative study with dupilumab.[7–9] Upadacitinib is approved in multiple countries for the treatment of AD in adults and adolescents. The objective of this analysis was to assess the efficacy of upadacitinib at Week 16 across patient subgroups using data from three phase 3 studies.

METHODS

Patients or participants

Detailed descriptions of the study designs and patient populations were previously reported.[7,8] Eligible patients included adolescents (aged 12–17 years, body weight ≥ 40 kg) and adults (aged 18–75 years) with moderate-to-severe AD who were candidates for systemic therapy (e.g. patients with inadequate response to topical AD treatments, patients who were using systemic AD treatment or patients for whom topical AD treatments were medically inadvisable).

Study design and treatment

Data from the phase 3, randomized, double-blind, placebo-controlled, multicentre studies—Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422) and AD Up (NCT03568318)—were used for this analysis. An integrated dataset was generated using data from the two identically designed monotherapy studies, Measure Up 1 and Measure Up 2; patients were randomized to receive once daily oral upadacitinib 15 mg, upadacitinib 30 mg, or placebo. Data from the combination therapy study (concomitant TCS use), AD Up, were analysed separately; patients were randomized to receive once daily oral upadacitinib 15 mg + TCS, upadacitinib 30 mg + TCS or placebo + TCS. To ensure transparent safety reporting and to capture safety trends with a larger patient population, safety data through 16 weeks from patients enrolled in a phase 2b placebo-controlled study (NCT02925117) were included in this safety assessment.

Assessments

Efficacy assessment

Skin clearance was assessed by the proportion of patients who achieved at least a 75% improvement in Eczema Area and Severity Index (EASI) from baseline (EASI 75), a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) response (scores of 0 [clear] or 1 [almost clear] with ≥2-grade reduction from baseline), and at least a 90% improvement in EASI from baseline (EASI 90) at Week 16. Improvement in itch was assessed by the proportion of patients who achieved a 4-point or greater improvement (reduction) from baseline in Worst Pruritus Numerical Rating Scale (WP-NRS reduction ≥ 4) among patients with a baseline WP-NRS score of ≥4 and a WP-NRS score of 0/1 among patients with a baseline WP-NRS score > 1 at Week 16. Efficacy was assessed according to the following subgroups: age (<18, 18 to 64, and ≥65 years), sex (female and male), race (Asian, Black and White), BMI (<25, 25 to <30 and ≥30 kg/m^2), weight quintiles, duration of disease (<10 and ≥10 years), immunoglobulin E levels (<200 and ≥200 kIU/L), baseline vIGA-AD (score of 3 [moderate] and 4 [severe]), baseline body surface area involvement (BSA; quartiles), history of atopic comorbidities (yes and no), history of asthma (yes and no), previous systemic therapy (with and without) and previous cyclosporine treatment (yes and no). To assess the potential effect of individual baseline characteristics, interaction p values were calculated for each endpoint.

Safety assessment

Although safety was not a focus of this subgroup analysis, overall safety data were collected during the trials.

Statistical analysis

Categorical endpoints were analysed using the Cochran–Mantel–Haenszel method adjusted by selected stratification factors. Non-response imputation incorporating multiple imputation for handling missing data due to COVID-19 (NRI-C) was used to analyse the intercurrent events or missing data.

RESULTS

Patients

Across the three trials, 2583 patients were randomized and received treatment. In the Measure Up 1 and Measure Up 2 studies, 1683 patients received upadacitinib 15 mg ($n = 557$), upadacitinib 30 mg ($n = 567$) or placebo ($n = 559$; Figure 1). In the AD Up study, 900 patients received upadacitinib 15 mg + TCS ($n = 300$), upadacitinib 30 mg + TCS ($n = 297$) or placebo + TCS ($n = 303$; Figure S1). Patient demographics and baseline disease characteristics were similar between treatment arms within the integrated monotherapy and concomitant TCS subgroup analyses (Table 1).

Skin clearance

The adjusted response difference compared with placebo in EASI 90 at Week 16 was 29.5% (95% CI 22.8%–36.3%; $p < 0.001$) to 41.1% (95% confidence interval [CI] 36.5%–45.7%; $p < 0.001$) in the overall study population treated with upadacitinib 15 mg (with or without TCS) and 49.9% (95% CI 43.3%–56.4%; $p < 0.001$) to 55.5% (95% CI 51.0%–60.0%; $p < 0.001$) treated with upadacitinib 30 mg (with or without TCS). The adjusted response difference compared with placebo in EASI 90 across subgroups was generally consistent with these ranges (Figure 2, Figure S2 and Table S1). The proportion of patients who achieved EASI 90 when treated with either dose of upadacitinib was higher than was the proportion of patients who achieved EASI 90 who received placebo (nominal $p \leq 0.05$; except for patients aged ≥65 years treated with upadacitinib 15 mg + TCS [40.0% vs. 22.1%], and Black patients treated with upadacitinib 15 mg + TCS [27.4%

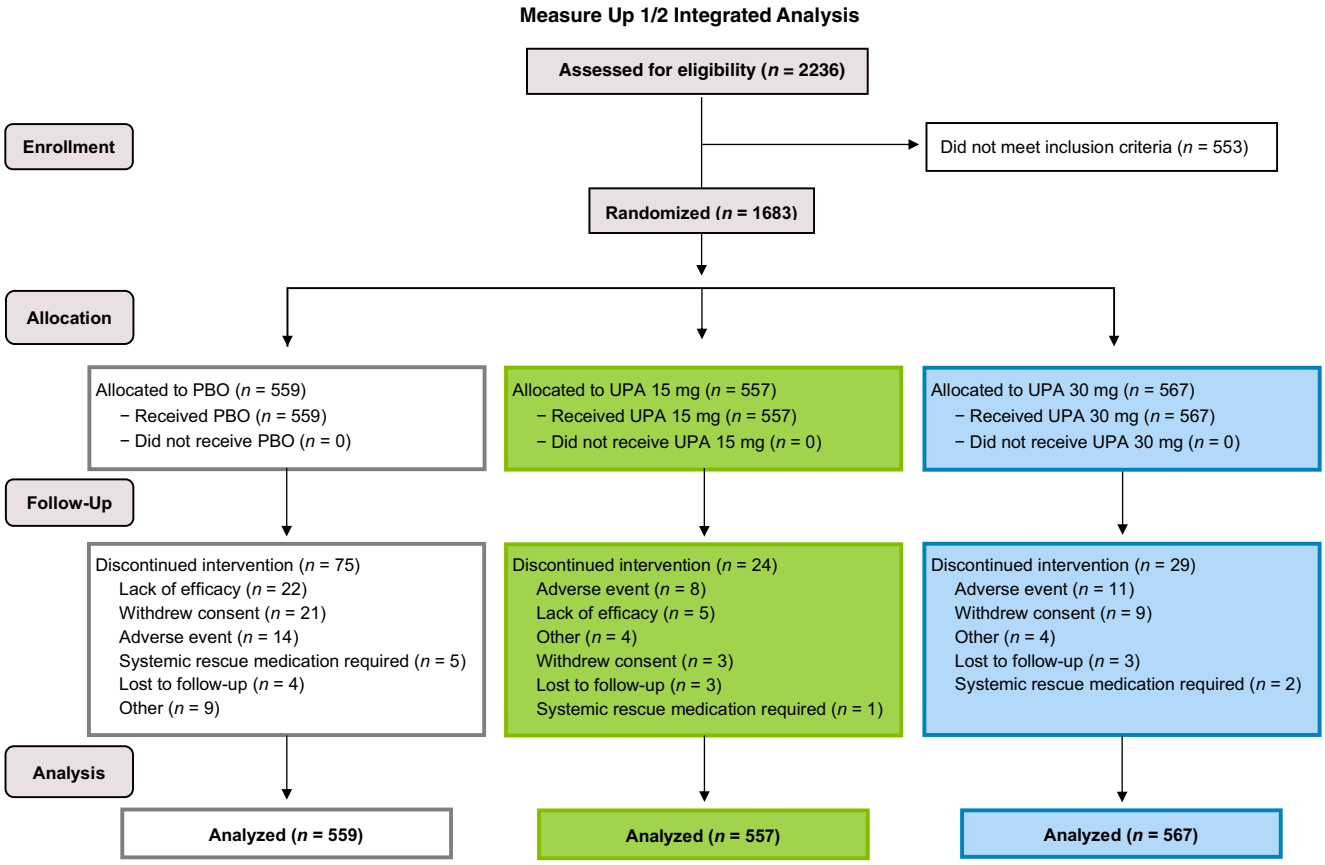

FIGURE 1 CONSORT diagram for the Measure Up 1 and 2 studies. Only the primary reasons given for discontinuation are listed. PBO, placebo; UPA, upadacitinib.

TABLE 1 Baseline demographics and characteristics.[a]

Parameter	Measure Up 1 and Measure Up 2 Studies			AD Up Study + TCS		
	UPA 15 mg (*n* = 557)	UPA 30 mg (*n* = 567)	PBO (*n* = 559)	UPA 15 mg (*n* = 300)	UPA 30 mg (*n* = 297)	PBO (*n* = 304)
Sex, *n* (%)						
Female	245 (44.0)	250 (44.1)	261 (46.7)	121 (40.3)	107 (36.0)	126 (41.4)
Male	312 (56.0)	317 (55.9)	298 (53.3)	179 (59.7)	190 (64.0)	178 (58.6)
Age, median (range), year	29.0 (12–74)	29.0 (12–75)	30.0 (12–75)	28.0 (13–74)	31.0 (12–72)	31.0 (12–75)
Age, years, *n* (%)						
<18	75 (13.5)	77 (13.6)	76 (13.6)	39 (13.0)	37 (12.5)	40 (13.2)
18–64	454 (81.5)	456 (80.4)	461 (82.5)	256 (85.3)	243 (81.8)	250 (82.2)
≥65	28 (5.0)	34 (6.0)	22 (3.9)	5 (1.7)	17 (5.7)	14 (4.6)
Race, *n* (%)						
White	366 (65.7)	389 (68.6)	377 (67.4)	204 (68.0)	218 (73.4)	225 (74.0)
Black	43 (7.7)	26 (4.6)	37 (6.6)	19 (6.3)	13 (4.4)	18 (5.9)
Asian	128 (23.0)	133 (23.5)	125 (22.4)	64 (21.3)	61 (20.5)	60 (19.7)
BMI, mean (SD), kg/m^2	25.8 (5.9)	25.8 (5.8)	26.5 (6.0)	25.8 (6.2)	25.7 (5.4)	25.9 (5.7)
BSA involvement, mean % (SD)	46.8 (22.3)	47.0 (22.6)	46.6 (22.2)	46.7 (21.6)	48.5 (23.1)	48.6 (23.1)
vIGA-AD score, *n* (%)						
3 (moderate)	280 (50.3)	280 (49.4)	281 (50.3)	143 (47.7)	140 (47.1)	141 (46.4)
4 (severe)	277 (49.7)	287 (50.6)	278 (49.7)	157 (52.3)	157 (52.9)	163 (53.6)
EASI score, mean (SD)	29.6 (12.3)	29.3 (11.7)	29.0 (12.4)	29.2 (11.8)	29.7 (11.8)	30.3 (13.0)
Weekly WP-NRS score, mean (SD)	7.2 (1.6)	7.3 (1.5)	7.3 (1.6)	7.1 (1.8)	7.4 (1.6)	7.1 (1.6)
Medical history, *n* (%)						
Acne	56 (10.1)	67 (11.8)	47 (8.4)	26 (8.7)	21 (7.1)	21 (6.9)
Asthma	220 (39.5)	221 (39.0)	230 (41.1)	130 (43.3)	140 (47.1)	138 (45.4)
Chronic sinusitis	2 (0.4)	2 (0.4)	0	1 (0.3)	2 (0.7)	0
Allergic conjunctivitis	28 (5.0)	31 (5.5)	21 (3.8)	22 (7.3)	17 (5.7)	21 (6.9)
Eosinophilic esophagitis	1 (0.2)	1 (0.2)	5 (0.9)	2 (0.7)	3 (1.0)	0
Food allergy	165 (29.6)	183 (32.3)	160 (28.6)	112 (37.3)	101 (34.0)	89 (29.3)
Nasal polyps	6 (1.1)	11 (1.9)	16 (2.9)	5 (1.7)	7 (2.4)	3 (1.0)
Allergic rhinitis	180 (32.3)	197 (34.7)	195 (34.9)	96 (32.0)	104 (35.0)	108 (35.5)
Previous systemic therapy,[b] *n* (%)	275 (49.4)	274 (48.3)	300 (53.7)	171 (57.0)	172 (57.9)	157 (51.6)
Previous cyclosporin, n (%)	124 (22.3)	103 (18.2)	117 (20.9)	65 (21.7)	67 (22.6)	66 (21.8)

Abbreviations: BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS, Worst Pruritis Numerical Rating Scale.

[a]Data are *n* (%), mean (range), or mean (SD).

[b]Systemic therapy included both biologic and non-biologic systemic therapies.

vs. 16.7%]). EASI 90 achievement was numerically higher across most subgroups for patients treated with upadacitinib 30 mg than for those treated with upadacitinib 15 mg.

The adjusted response difference compared with placebo in proportions of patients achieving EASI 75 at Week 16 across subgroups, regardless of treatment, was generally consistent with the overall study population results (upadacitinib 15 mg, 38.1% [95% CI 30.8%–45.4%; $p < 0.001$] to 50.1% [95% CI 45.2%–55.0%; $p < 0.001$]; upadacitinib 30 mg, 50.6% [95% CI 43.8%–57.4%; $p < 0.001$] to 61.5% [95% CI 57.0%–66.1%; $p < 0.001$]) (Figure S3 and Table S2). Across most subgroups, greater proportions of patients achieved EASI 75 with upadacitinib 30 mg or upadacitinib 15 mg than with placebo (nominal $p \leq 0.05$; except for patients aged ≥65 years treated with upadacitinib 15 mg + TCS [60.0% vs. 37.1%], and Black patients treated

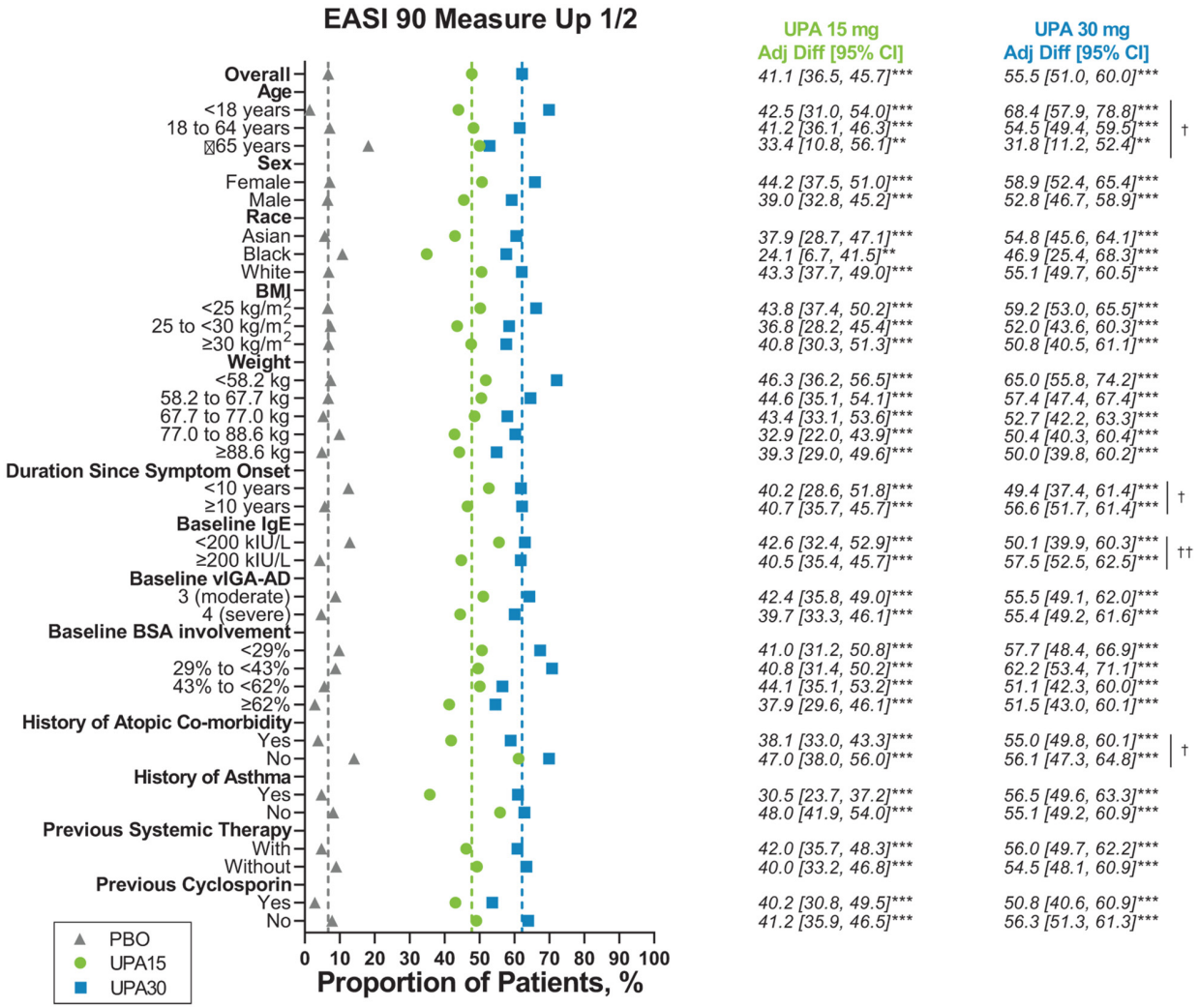

FIGURE 2 Proportion of patients achieving EASI 90 in the Measure Up 1 and Measure Up 2 integrated analysis at Week 16 (UPA30 and UPA15 vs. PBO). Nominal p values: *$p \le 0.05$, **$p \le 0.01$, ***$p \le 0.001$. Interaction p values: $^{\dagger}p \le 0.05$, $^{\dagger\dagger}p \le 0.01$. Non-responder imputation incorporating multiple imputation for handling missing data due to COVID-19 was used. Dashed lines represent the overall response rates for patients receiving each dose. Adj Diff, adjusted difference; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; IgE, immunoglobulin E; PBO, placebo; UPA15, upadacitinib 15 mg; UPA30, upadacitinib 30 mg; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

with either dose of upadacitinib + TCS [53.8% and 61.4% for upadacitinib 30 mg and upadacitinib 15 mg, respectively, vs. 44.4% for placebo]). The proportions of patients who achieved EASI 75 were numerically higher in most subgroups for patients treated with upadacitinib 30 mg than for patients treated with upadacitinib 15 mg.

The adjusted response difference compared with placebo in proportions of patients achieving vIGA-AD 0/1 at Week 16 across subgroups was also consistent with the results from the overall study population (upadacitinib 15 mg, 28.5% [95% CI 22.1%–34.9%; $p < 0.001$] to 36.8% [95% CI 32.3%–41.4%; $p < 0.001$]; upadacitinib 30 mg, 47.6% [95% CI 41.1%–54.0%; $p < 0.001$] to 50.4% [95% CI 45.9%–54.9%; $p < 0.001$]; Figure S4 and Table S3). Generally, a higher proportion of patients achieved vIGA-AD 0/1 when treated with either dose of upadacitinib than among patients receiving placebo (nominal $p \le 0.05$; except for patients aged ≥65 years treated with upadacitinib 15 mg + TCS [40.0% vs. 14.3%], and Black patients treated with upadacitinib 15 mg + TCS [31.6% vs. 11.1%]). The proportion of patients who achieved vIGA-AD 0/1 was numerically higher in most subgroups for patients treated with upadacitinib 30 mg than for those treated with upadacitinib 15 mg. Generally, interaction p values indicated that baseline IgE and disease duration since symptom onset may have had an effect on the skin clearance efficacy of upadacitinib 30 mg, though the same trend was not observed for the upadacitinib 15 mg dose.

Improvement in itch

At Week 16, improvement in itch across subgroups was consistent with the results from the overall study population. The proportions of patients who achieved WP-NRS of 0/1

when treated with either dose of upadacitinib were higher than for patients who received placebo (nominal $p \leq 0.05$; except for patients aged ≥65 years treated with upadacitinib 15 mg + TCS [60.0% vs. 14.3%] or upadacitinib 30 mg + TCS [41.2% vs. 14.3%], and Black patients treated with upadacitinib 30 mg + TCS [33.3% vs. 16.7%]; Figure 3, Figure S5, and Table S4).

Higher proportions of patients achieved WP-NRS reduction ≥4 from baseline when treated with either dose of upadacitinib than did patients receiving placebo (nominal $p \leq 0.05$; except for patients aged ≥65 years treated with upadacitinib 15 mg + TCS [60.0% vs. 15.4%], and Black patients treated with upadacitinib 30 mg + TCS [41.7% vs. 27.8%]; Figure S6 and Table S5). The proportion of patients who achieved WP-NRS reduction ≥4 from baseline was numerically higher in most subgroups for patients treated with upadacitinib 30 mg than for those treated with upadacitinib 15 mg. Generally, interaction p values indicated that baseline IgE and disease duration since symptom onset may have had an effect on achievement of WP-NRS reduction ≥4 in patients receiving upadacitinib 30 mg; the same trend was not observed for the upadacitinib 15 mg dose, nor for the achievement of WP-NRS of 0/1 (for either dose).

Safety

The safety of upadacitinib during the double-blind period (Week 16) in the Measure Up 1, Measure Up 2 and AD Up studies have been reported previously.[7,8] Among the patients

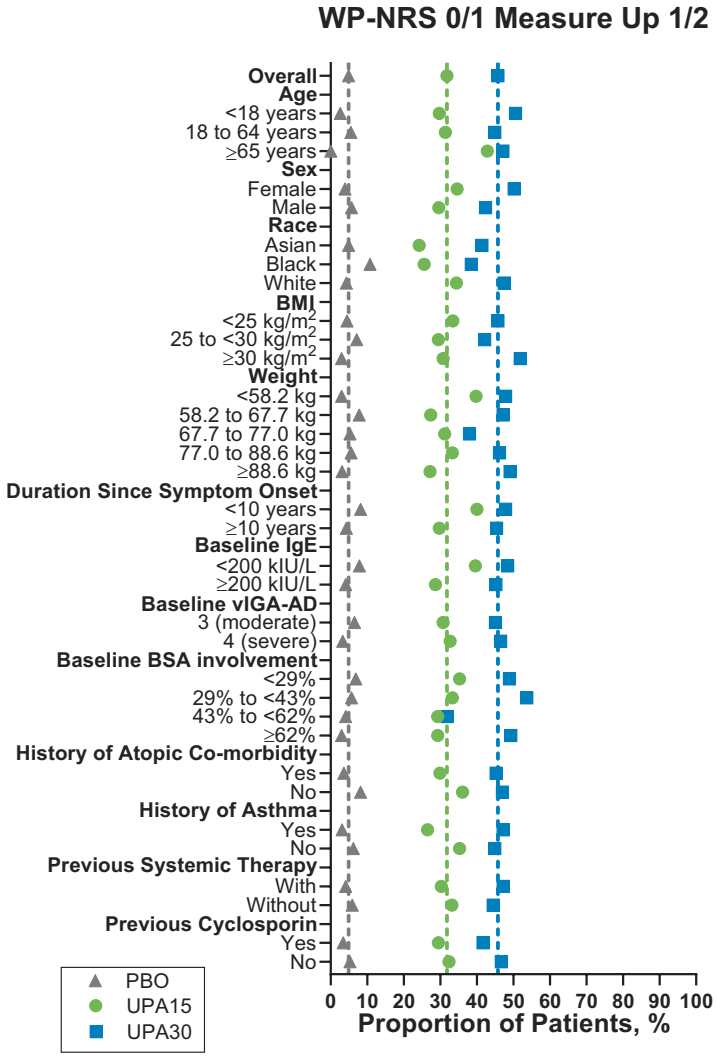

FIGURE 3 Proportion of patients achieving WP-NRS 0/1 at Week 16 for patients with WP-NRS > 1 at baseline in the Measure Up 1 and Measure Up 2 integrated analysis (UPA30 and UPA15 vs. PBO). Nominal p values: *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. Non-responder imputation incorporating multiple imputation for handling missing data due to COVID-19 was used. WP-NRS weekly averages were used. Dashed lines represent the overall response rates for patients receiving each dose. Adj Diff, adjusted difference; BMI, body mass index; BSA, body surface area; IgE, immunoglobulin E; PBO, placebo; UPA15, upadacitinib 15 mg; UPA30, upadacitinib 30 mg; WP-NRS, Worst Pruritus Numerical Rating Scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

with moderate-to-severe AD enrolled in these clinical trials, upadacitinib was well tolerated with no increase in adverse events (AEs) leading to treatment discontinuation or serious AEs compared with placebo. The most commonly reported AE was acne, which was mild or moderate in severity in all but one patient. Most elevations in creatinine phosphokinase levels were asymptomatic; one patient in the upadacitinib 15-mg group developed rhabdomyolysis after jet skiing.

Subgroup analyses were performed to determine whether older patients may be at higher risk of AEs including serious infection when treated with upadacitinib (Table 2). Serious AEs, severe AEs and AEs leading to treatment discontinuation were higher in patients aged ≥65 years compared with patients aged <65 years, regardless of upadacitinib dose or treatment with placebo. Though the number of patients aged ≥65 years was limited, no consistent pattern was observed regarding the risk of AEs including serious infection.

Possible risk factors for herpes zoster were examined including age and geographical region (Table 3). In adolescents, the incidence of herpes zoster was higher with upadacitinib 30 mg than with upadacitinib 15 mg. No serious events of herpes zoster were reported in adolescents or adults. No clear risk for herpes zoster by age was noted; a small sample size could have affected the assessment of the risk of herpes zoster in patients aged ≥65 years. A higher incidence of herpes zoster was reported for study sites in Asia than for the incidence of herpes zoster at sites in the rest of the world. No patient discontinued the study drug because of herpes zoster infection.

The incidence of acne was higher in adolescents and younger adults than in older adults (Table 3). Although acne occurred more frequently in adolescents and younger adults, no events of acne were serious, and only one occurrence of acne in the upadacitinib 30-mg group was severe. More than

TABLE 2 Incidence of treatment-emergent adverse events by age group.

	Patients, *N* (%)[a]					
	Aged <65 years			Aged ≥65 and ≤75 years		
Adverse event	UPA 15 mg *N* = 863	UPA 30 mg *N* = 852	PBO *N* = 861	UPA 15 mg *N* = 36	UPA 30 mg *N* = 54	PBO *N* = 41
Overview						
All TEAEs	550 (63.7)	588 (69.0)	503 (58.4)	24 (66.7)	42 (77.8)	25 (61.0)
AE with reasonable possibility of being drug-related	289 (33.5)	349 (41.0)	182 (21.1)	9 (25.0)	18 (33.3)	3 (7.3)
Severe AEs	41 (4.8)	38 (4.5)	39 (4.5)	2 (5.6)	4 (7.4)	4 (9.8)
Serious AEs	17 (2.0)	15 (1.8)	23 (2.7)	2 (5.6)	4 (7.4)	3 (7.3)
AEs leading to discontinuation	20 (2.3)	21 (2.5)	30 (3.5)	1 (2.8)	5 (9.3)	4 (9.8)
Deaths	0	0	0	0	0	0
Adverse events of special interest						
Serious infection	6 (0.7)	4 (0.5)	5 (0.6)	1 (2.8)	0	0
Herpes zoster	14 (1.6)	14 (1.6)	5 (0.6)	0	0	0
Eczema herpeticum[b]	6 (0.7)	6 (0.7)	4 (0.5)	0	1 (1.9)	0
Active tuberculosis	0	0	0	0	0	0
NMSC	3 (0.3)	2 (0.2)	0	0	0	0
Malignancy excluding NMSC	0	1 (0.1)	0	0	3 (5.6)	0
Lymphoma	0	1 (0.1)	0	0	0	0
Adjudicated MACE	0	0	0	0	0	0
Adjudicated VTE	0	0	1 (0.1)	0	0	0
Hepatic disorders	15 (1.7)	15 (1.8)	12 (1.4)	0	0	0
Cytopenia						
Anaemia	1 (0.1)	6 (0.7)	3 (0.3)	2 (5.6)	7 (13.0)	1 (2.4)
Neutropenia	10 (1.2)	24 (2.8)	3 (0.3)	0	2 (3.7)	0
Lymphopenia	2 (0.2)	2 (0.2)	3 (0.3)	0	1 (1.9)	0
CPK elevation	40 (4.6)	50 (5.9)	21 (2.4)	1 (2.8)	0	0

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event, defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; NMSC, non-melanoma skin cancer; PBO, placebo; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic event, defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

[a]Includes patients from all 3 placebo-controlled phase 3 trials (Measure Up 1, Measure Up 2, and AD Up) and the phase 2b placebo-controlled trial.

[b]All opportunistic infections excluding TB and herpes zoster were reported as eczema herpeticum or its synonymous Kaposi's varicelliform eruption.

TABLE 3 Incidence of acne and herpes zoster by subgroup.

Parameter	Patients, *n/N* (%)[a]		
	UPA 15 mg	UPA 30 mg	PBO
Herpes zoster			
Age			
<18 years	1/114 (0.9)	3/114 (2.6)	0/115
18–40 years	11/509 (2.2)	9/495 (1.8)	3/486 (0.6)
40–65 years	2/240 (0.8)	2/243 (0.8)	2/260 (0.8)
≥65 years	0/36	0/54	0/41
Geographical region			
Asia	2/114 (1.8)	4/122 (3.3)	2/106 (1.9)
Rest of world	12/785 (1.5)	10/784 (1.3)	3/796 (0.4)
Acne			
Age			
<18 years	15/114 (13.2)	17/114 (14.9)	1/115 (0.9)
18–40 years	55/509 (10.8)	90/495 (18.2)	15/486 (3.1)
40–65 years	16/240 (6.7)	27/243 (11.1)	4/260 (1.5)
≥65 years	0/36	3/54 (5.6)	0/41
Sex			
Female	45/378 (11.9)	67/377 (17.8)	5/402 (1.2)
Male	41/521 (7.9)	70/529 (13.2)	15/500 (3.0)
Race			
White	48/591 (8.1)	80/630 (12.7)	10/629 (1.6)
Non-White	38/308 (12.3)	57/276 (20.7)	10/273 (3.7)

Abbreviations: PBO, placebo; UPA, upadacitinib.

[a]Includes patients from all 3 placebo-controlled phase 3 trials (Measure Up 1, Measure Up 2, and AD Up) and the phase 2b placebo-controlled trial.

90% of acne cases involved the face; the primary morphology of the acne was inflammatory papules, pustules and comedones.

DISCUSSION

At Week 16, placebo-corrected response rates in skin clearance and improvement in itch were generally similar across populations stratified by age, sex, race, BMI, weight quintile, AD severity, BSA involvement, baseline immunoglobulin E levels, duration of disease, history of atopic comorbidities or asthma, and previous exposure to systemic therapy including cyclosporin. Currently, there is no biomarker that has been identified as a predictor of response to upadacitinib in patients with moderate-to-severe AD. Efficacy across subgroups was comparable to that seen in the overall population. Generally, skin clearance and improvement in itch were greater for patients treated with upadacitinib 30 mg than for patients treated with upadacitinib 15 mg. Additionally, the difference in response rate from placebo of receiving upadacitinib 30 mg vs. upadacitinib 15 mg for both skin clearance and itch efficacy endpoints trends larger for patients with atopic comorbidities, history of asthma, baseline immunoglobulin E ≥ 200 kIU/L, or ≥10 years since symptom onset (Figures 2 and 3, Figures S2–S6). Weight effected EASI 75 (Figure S3 and Table S2), EASI 90 (Figure 2, Figure S2 and Table S1) and WP-NRS 0/1 (Figure 3, Figure S5, and Table S4); patients in the highest weight quintile generally had worse outcomes than did patients with lower weights, regardless of treatment group. Additionally, Black patients generally had lower response rates than did Asian and White patients, though statistical significance was not achieved, possibly due to low representation of Black patients in these studies or with the known challenges in severity scoring in darker skin types (e.g. erythema can be more difficult to detect in patients with skin of colour).[10] Duration since symptom onset and baseline IgE consistently had an effect on the treatment benefit of upadacitinib 30 mg, but this same trend was not observed for upadacitinib 15 mg. While small sample sizes and lack of multiplicity control limit the ability to quantitatively compare dose-related differences across subgroups, the pattern of patients with more severe or harder-to-treat AD deriving additional benefit from a higher dose of upadacitinib, with or without TCS use, is one that could be explored in future studies.

Upadacitinib was generally well tolerated with no consistent pattern of AE risk including serious infection in patients aged ≥65 years. There was an increased incidence of herpes zoster infection among patients in Asia than in the rest of the world, and acne was reported more frequently among adolescents and younger adults than in older adults. An in-depth safety analysis of upadacitinib based on integrated data from the three phase 3 clinical trials was previously reported,[11] as was a post hoc analysis that characterized acne reported among patients enrolled in the trials.[12] Notably, all the investigators for these studies were dermatologists who may have been more likely to identify acne as an AE than would general practitioners.

Given the heterogeneity of the disease, management of AD may be different across subgroups of patients. For example, treatment of AD in older adults may be challenging because of their higher number of non-atopic comorbidities and greater medication use than in younger adults and adolescents.[13] Black patients are disproportionately affected by AD compared with Asian and White patients; lichenification is a more common presentation of AD in Black patients.[10] Furthermore, differences in drug pharmacokinetics may alter response and safety profiles across racial and ethnic groups.

Although some patient subgroups remain underrepresented in randomized clinical trials, an analysis of clinical response across multiple subgroups may provide insight on potential treatment response differences. Treatment recommendations for some immune-mediated inflammatory skin conditions, such as psoriasis, are influenced by the patient's age, weight, presence of comorbidities and previous systemic therapy use.[4]

To our knowledge, our report is the first multiple subgroup analysis based on randomized clinical trial data from patients with moderate-to-severe AD treated with systemic therapy. Dupilumab has been reported to be effective across racial groups[14] and in different age groups (children,[15] adults[16] and in adolescents with prior systemic therapy[17])

but has not been fully or systematically investigated across multiple subgroups based on sex, age, BMI, baseline AD involvement, prior treatment or presence of non-atopic comorbidities. We found no reports of a multiple subgroup analysis for conventional systemic AD therapies, including cyclosporine, methotrexate, or azathioprine, nor for other AD systemic therapies including abrocitinib, baricitinib, cyclosporine or tralokinumab.

This analysis was not without limitations. First, the modest patient numbers in some subgroups based on age, race and baseline BSA make it difficult to definitively conclude upadacitinib provides comparable skin clearance and improvement in itch among those subgroups. Second, some endotypes of AD (e.g. colonization by *Staphylococcus aureus*) that are not characterized here may have an influence on response.[1] Finally, no clinical phenotyping was performed for these studies.

These results support upadacitinib as a suitable treatment option for moderate-to-severe AD in a wide variety of patients given its high and consistent skin clearance rates across all subgroups analysed through Week 16.

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CONFLICT OF INTEREST STATEMENT

JPT is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, Coloplast, OM Pharma, Aslan Pharmaceuticals, Union Therapeutics, Eli Lilly, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme. He is a speaker for AbbVie, Almirall, Eli Lilly, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme, and has received research grants from Pfizer, Regeneron and Sanofi-Genzyme. DT has been a consultant and advisor and/or has received speaking fees and/or grants and/or served as an investigator in clinical trials for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galapagos, Galderma, LEO Pharma, Janssen-Cilag, Kirin, L'Oréal, Novartis, Pfizer, Regeneron, Samsung, Sanofi, Regeneron and UCB. TB is an advisor, speaker and researcher for AbbVie, Affibody, Almirall, AnaptysBio, Arena, Asana Biosciences, ASLAN pharma, Bayer Health, BioVerSys, Boehringer Ingelheim, Bristol-Myers Squibb, Connect Pharma, Celgene, Daiichi Sankyo, Dermavant, Domain Therapeutics, DS Biopharma, EQRx, RAPT Therapeutics (FLX Bio), Galapagos/MorphoSys, Galderma, Glenmark, GlaxoSmithKline, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, Lilly, L'Oréal, Menlo Therapeutics, Novartis, Numab, OMPharma, Pfizer, Pierre Fabre, Sanofi/ Regeneron, Q32bio, RAPT and UCB. He is a founder of the non-profit biotech company 'Davos Biosciences' within the International Kühne-Foundation. MG has been an investigator, speaker, advisor or consultant for AbbVie, Amgen, Akros, Arcutis, AnaptysBio, Aslan, Aristea, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin Pharma, LEO Pharma, Medimmune, Merck, Meiji, Moonlake, Nimbus, Novartis, Pfizer, Roche, Regeneron, Sanofi Genzyme, Sun Pharma, UCB and Valeant/Bausch. MdB-W has been a consultant, advisory board member and/or speaker for AbbVie, Almirall, Arena, ASLAN, Eli Lilly, Galderma, Janssen, LEO Pharma, Pfizer, Regeneron and Sanofi Genzyme. WS is a consultant for AbbVie, Genentech, LEO, Lilly, Novartis, Pfizer, Regeneron and Sanofi. He is a speaker for AbbVie, LEO, Pfizer, Regeneron and Sanofi, and has received research grants from AbbVie, ASLAN, Genentech, Incyte, LEO Pharma, Regeneron and Sanofi. KK has received consulting fees, honoraria, grant support or lecturing fees from AbbVie, Japan Tobacco, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Procter & Gamble, Sanofi, Taiho Pharmaceutical and Torii Pharmaceutical. SB is an investigator or speaker for Almirall, Sanofi Genzyme, AbbVie, Novartis, Janssen, LEO Pharma, Pfizer, Eli Lilly and UCB Pharma. PCL has been an investigator or speaker and has received consulting fees, honoraria, grant support or lecturing fees from Pierre Fabre Laboratory, Beiersdorf, Laboratoire La Roche Posay, Sanofi Genzyme, AbbVie, Novartis, Janssen, Pfizer and Elli Lilly. JX is an investigator for AbbVie, Boehringer Ingelheim, LEO Pharma, Janssen-Cilag, Novartis, Pfizer and Sanofi. XH, YL, EMR, BMC, CN and AG are full-time employees of AbbVie Inc. and may hold AbbVie stock and/or stock options. ELS received personal fees from AbbVie, Anacor, Bausch Health (Valeant), Boehringer Ingelheim, Dermavant, Forté Pharma, Incyte, Lilly, LEO Pharma, MedImmune, Menlo Therapeutics, Pfizer, Pierre Fabre, Regeneron, Roivant, and Sanofi. He has received grants from AbbVie, Amgen, Celgene, Chugai, Galderma, Genentech, Kyowa Kirin, Lilly, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Sanofi, Tioga Pharmaceuticals and Vanda.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis data sets), as well as other information (e.g. protocols, clinical study reports or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any

qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.html.

IRB APPROVAL STATUS

Independent ethics committees or institutional review boards approved the study protocols, informed consent forms and recruitment materials before patient enrolment.

ORCID

J. P. Thyssen https://orcid.org/0000-0003-3770-1743
M. Gooderham https://orcid.org/0000-0001-8926-0113
S. Barbarot https://orcid.org/0000-0002-6629-9100
B. M. Calimlim https://orcid.org/0000-0002-6463-6433
E. L. Simpson https://orcid.org/0000-0003-0853-0252

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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